IUCLID

Data Set

Existing Chemical	:	ID: 108-82-7
CAS No.	:	108-82-7
EINECS Name	:	2,6-dimethylheptan-4-ol
EC No.	:	203-619-6
TSCA Name	:	4-Heptanol, 2,6-dimethyl-
Molecular Formula	:	C9H20O

Producer related part

Company	:	TRS Inc.
Creation date	:	12.09.2003

Substance related part

Company	:	TRS Inc.
Creation date	:	12.09.2003
Status	:	
Memo	:	
Printing date	:	21.08.2006
Revision date	:	
Date of last update	:	21.08.2006
Number of pages	:	37
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	OC(CC(C)C)CC(C)C
Molecular formula	:	C9 H20 O1
Molecular weight	:	144.26
Petrol class	:	

05.12.2003

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	
Colour	:	Transparent colorless
Odour	:	Sweet
Remark	:	Purity/composition: >=70% 2,6-diemthyl-4-hepatanol (DIBC) <=30% 4,6-dimethyl-2-hepatnol (DMH) <=3% 2,6-dimethyl-4-heptanone

05.12.2003

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2,6-Dimethyl heptanol-4

04.12.2003

2,6-Dimethyl-4-heptanol

04.12.2003

4-Heptanol, 2,6-dimethyl-

04.12.2003

4-Hydroxy-2,6-dimethyl heptane

04.12.2003

Diisobutyl Carbinol

04.12.2003

Diisobutylcarbinol

04.12.2003

Nonyl alcohol, secondary

04.12.2003

sec-Nonyl alcohol

04.12.2003

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : = -65.2 °C

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
04.12.2003 (9)

2.2 BOILING POINT

Value : = 177.9 °C at 1013 hPa

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
04.12.2003 (9)

2.3 DENSITY

Type : density
Value : = .8112 g/cm³ at 20 °C

08.10.2003 (9)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .25955 hPa at 20 °C

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
04.12.2003 (9)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 3.08 at °C
pH value :
Method : other (calculated): EPIWIN (v 3.10) KOWWIN Submodel (v 1.66)
Year : 2003
GLP :
Test substance :

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg) = 0.19515;
Boiling point (deg C) = 177.85; and
Melting point (deg C) = -65.15.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
04.12.2003 (12)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 570 mg/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: Broadly covered by ASTM method E 1148
Year	:	2000
GLP	:	yes
Test substance	:	other TS

Remark : The liquid-liquid equilibrium measurements were performed in a 2.0 liter glass vessel submerged in a constant-temperature bath. Water and DIBC were added to this vessel through 1/16" lines. The mixture was then stirred vigorously by a magnetic stirrer at the desired bath temperature. Stirring produced very fine droplets of each phase entrained in the other phase, which slowly separated after the liquid was still. After the liquid phases had separated, three 20-30 gram samples were withdrawn from the aqueous liquid phase into weighed glass bottles. A weighed amount of a mixture of toluene and dodecane was added to each vial of the aqueous phase, and the DIBC was extracted into the toluene-rich phase by vigorously shaking the vial. Dodecane served as the internal standard. An aliquot of the toluene-rich phase was then analyzed by gas chromatography. The concentration of water was found by difference. The gas chromatographic analyses were performed by an HP5890 II gas chromatograph equipped with a DB-1 capillary column. The column was 30 meters long with an internal diameter of 0.32 millimeters and a film thickness of 3 micrometers. Response factors were determined by analyzing gravimetrically prepared standards before each set of samples.

Three 5-10 gram samples of the hydrocarbon phase were withdrawn into weighed syringes. The contents of each syringe were flushed into the Karl-Fisher titrator by first injecting as much liquid as possible from the syringe into the titrator vessel. Then a long needle was used to pull the titrant and solvent from the titration vessel into the syringe, shaking the syringe to mix the it, and then injecting the liquid back into the titration vessel. The sample was then titrated. The titrant was calibrated by titrating weighed aliquots of distilled water.

Result : In all samples there was excellent separation of the phases. Results were repeated in triplicate. Compositions between one weight percent and 0.1 wt% are estimated to be reliable to ±5% of the reported value. The uncertainty increases to ±20% of the reported value as the measured compositions decrease to the ppm level.

Test substance : 2,6-dimethyl-4-heptanol, DIBC
Purity > 96 wt%

Reliability : (1) valid without restriction
Comparable to guideline study.

Flag : Critical study for SIDS endpoint

05.12.2003 (14)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 65.9 °C
Type :

02.10.2003 (9)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	other: EPIWIN (v 3.10) AOPWIN Submodel (v 1.90)
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 6.9 hour(s)
Degradation	:	% after
Quantum yield	:	
Deg. product	:	
Method	:	other (calculated): EPIWIN (v 3.10) AOPWIN Submodel (v 1.90)
Year	:	2003
GLP	:	
Test substance	:	

Remark : Overall OH rate constant = 18.6802 E-12 cm3/molecule/sec
The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg) = 0.19515;
Boiling point (deg C) = 177.85; and
Melting point (deg C) = -65.15.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
05.12.2003 (10)

3.1.2 STABILITY IN WATER

Remark : Expert Statement: DIBC does not react with water; the only functionality other than carbon-carbon and carbon-hydrogen bonds is the hydroxyl group which does not hydrolyze.

04.12.2003

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media	:	other: air (emissions to compartment = 1000 kg/hr)
Method	:	Calculation according Mackay, Level III
Year	:	2003

Remark : The EPIWIN model was run using the following measured physical chemical properties:

Vapor pressure (mm Hg) = 0.19515;
Boiling point (deg C) = 177.85; and
Melting point (deg C) = -65.15.

Result : Concentration (%):
Air = 90
Water = 8
Soil = 2
Sediment = <1

Level III Fugacity Model (Full-Output):
==========

Chem Name : 4-Heptanol, 2,6-dimethyl-
Molecular Wt: 144.26
Henry's LC : 0.000129 atm-m3/mole (Henry database)
Vapor Press : 0.195 mm Hg (user-entered)
Log Kow : 3.08 (Kowwin program)
Soil Koc : 493 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	90.4	13.7	1000
Water	7.85	360	0
Soil	1.67	360	0
Sediment	0.0955	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	2.79e-011	831	165	83.1	16.5
Water	6.39e-012	2.75	1.43	0.275	0.143
Soil	1.24e-012	0.585	0	0.0585	0
Sediment	3.03e-012	0.00837	0.000348	0.000837	3.48e-005

Persistence Time: 18.2 hr
Reaction Time: 21.9 hr
Advection Time: 110 hr
Percent Reacted: 83.4
Percent Advected: 16.6

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 13.74
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.040 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
07.12.2003 (13)

Media : other: water (emissions to compartment = 1000 kg/hr)
Method : Calculation according Mackay, Level III
Year : 2003

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg) = 0.19515;
Boiling point (deg C) = 177.85; and
Melting point (deg C) = -65.15.

Result : Concentration (%)
Air = 1
Water = 97
Soil < 0.1
Sediment = 1

Level III Fugacity Model (Full-Output):
==========

Chem Name : 4-Heptanol, 2,6-dimethyl-
Molecular Wt: 144.26
Henry's LC : 0.000129 atm-m3/mole (Henry database)
Vapor Press : 0.195 mm Hg (user-entered)
Log Kow : 3.08 (Kowwin program)
Soil Koc : 493 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.38	13.7	0
Water	97.4	360	1000
Soil	0.0255	360	0
Sediment	1.18	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	6.35e-012	189	37.5	18.9	3.75
Water	1.18e-009	508	264	50.8	26.4
Soil	2.83e-013	0.133	0	0.0133	0
Sediment	5.59e-010	1.54	0.0642	0.154	0.00642

Persistence Time: 271 hr
Reaction Time: 388 hr
Advection Time: 899 hr
Percent Reacted: 69.9
Percent Advected: 30.1

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 13.74
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.040 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
07.12.2003 (13)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : other
Concentration : 33.4 mg/l related to
related to

Contact time	:	28 day(s)
Degradation	:	60 (±) % after 28 day(s)
Result	:	other
Kinetic of testsubst.	:	8 day(s) > 10 % 18 day(s) 18 % 28 day(s) 60 % % %
Control substance	:	Benzoic acid, sodium salt
Kinetic	:	28 day(s) > 90 % %
Deg. product	:	not measured
Method	:	OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
Year	:	2003
GLP	:	yes
Test substance	:	other TS
Method	:	This study investigated the biodegradation of the test substance in respirometers under aerobic conditions for 28 days. Duplicate 500-ml test solutions were prepared by adding mineral salts medium, reagent water, the activated sludge inoculum (6.0x106 CFU/ml) and test substance (added by weight) to 1-L flasks to achieve a nominal ThOD of 100 mg/l. Negative controls, abiotic controls (100 mgThOD/l) and reference controls (sodium benzoate, 60 mg/L or 100 mgThOD/l) were similarly prepared, only the negative control in duplicate, and concurrently maintained. The flasks were continuously stirred during incubation in water bath at 22±2°C in the dark. Oxygen in the sealed headspace above each solution was measured every 6 hours. The pH and DOC concentration were measured in each flask at test termination. Bacterial plate counts were performed for the prepared activated sludge and a sample of each test solution collected on Day 28. Due to the high DOC removal from the abiotic control, the test was repeated after changing selected parameters in an effort to reduce possible volatilization and improve the efficiency of the respirometer. The values reported herein reflect the results of the second test.
Remark	:	Activated sludge suspension was collected from aeration basin #1 of the Columbia Wastewater Treatment Plant, Columbia, Missouri.
Result	:	The pH in all of the flasks ranged from 7.23 to 7.39, and averaged 7.37 and 7.23 in the test substance replicates at initiation and termination, respectively. The bacterial plate counts at termination showed that the test substance solutions contained an average of 1.12x105 CFU/ml. Degradation based on DOC removal reached 99.5% by Day 28. The percent ThOD exceeded 10% ThOD by Day 8 in both replicates and further degraded to an average 53% ThOD by Day 18 (the end of the 10-day window). By test termination, ThOD reached 60%, thus this test substance is considered to be not readily biodegradable under the conditions of this test in spite of the rapid biodegradation phase between days 7 and 11 and almost complete removal of DOC. Since volatilization was minimized during this test, the additional 40% difference in biodegradation seen as DOC removal was attributed to adsorption. This conclusion was supported by the 56% degradation as DOC removal observed for the sterile control (versus the 7.2% ThOD). The percent ThOD for the reference substance was >90% by Day 28, proving that the inoculum was viable.
Test substance	:	See Section 1.1; Purity: DIBC + DMH = 99.4%; The purity of the test substance was not included in the report but the Lot Number used was the same as for the Acute Fish Toxicity and Acute Invertebrate Toxicity studies for which the purity was determined.
Conclusion	:	Not readily biodegradable under the conditions of this test, as '10-day window' was not met (Author of report). DIBC can be classified as

inherently biodegradable (Sponsor).

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.12.2003 (3)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= 3.44 measured/nominal
LC50	:	= 28.6 measured/nominal
Limit test	:	
Analytical monitoring	:	no
Method	:	EPA OTS 797.1400
Year	:	2002
GLP	:	yes
Test substance	:	other TS

Method : This study evaluated the acute toxicity of the test substance to rainbow trout (Onchorynchus mykiss Walbaum) over a 96-hour exposure period under static conditions. A preliminary study found 100% mortality at nominal concentrations of 50 and 100 mg DIBC/L and no deaths at 2.5 or 25 mg/L after 96 hr. Based on this preliminary study, the test solutions for the definitive study were prepared in duplicate at nominal concentrations of 3.44, 6.19, 11.1, 20.1, 36.1 and 65.0 mg/l. All concentrations were prepared without correction for purity. Duplicate negative control solutions (dilution water) were maintained concurrently. Dilution water was Lake Huron water supplied to the laboratory by the City of Midland Water Treatment Plant, subsequently sand-filtered, pH-adjusted with gaseous CO2, carbon-filtered and UV-irradiated, and monitored regularly. The dilution water used in this study was characterized as follows: TOC < 1000 ug/L, hardness of 72 mg/l as CaCO3, alkalinity of ~42 mg/l as CaCO3, pH of 7.3, conductivity of 190 mmhos/cm and chlorine <1 mg/l. Test vessels were 12-l glass beakers which were filled with 10 l of test solution. Ten fish were impartially introduced to each replicate test vessel at test initiation. Loading did not exceed 0.5-g fish per liter of test solution. Fish were not fed during the study. Terminal body weight and standard length were recorded for all surviving fish at test termination. Fish were observed daily for mortality and sublethal effects. Mortality was defined as a lack of response to prodding of the caudal peduncle accompanied by an absence of opercular movement. Dissolved oxygen, pH and temperature were recorded at test initiation and daily thereafter.

The U.S. EPA Trimmed Spearman-Karber Program, v. 1.5, using nominal DIBC concentrations was used to calculate the LC50 values and corresponding percent trim values. The NOEC was determined as the highest exposure concentration that exhibited 0% mortality or sublethal effects.

Remark : Mortality in the 65, 36.1 and 6.19 mg/l treatment groups was 100, 85 and 5% after 72 and 96 hours of exposure. No deaths occurred at 11.1 or 20.1 mg/L. Sublethal effects at 6.19 to 36.1 mg/L included partial to complete loss of equilibrium, lethargy and immobility. The temperature, pH and dissolved oxygen concentration during this study were maintained at 12.3 ± 0.2°C, 7.0 ± 0.3 and 9.2 ± 0.6 mg/l (or >72% saturation), respectively. Pooled standard length and weight means (± sd) for all surviving fish (treatments and controls) were 35 ± 2 mm and 518 ± 110 mg, respectively.

Result : LC50 (24-hr) = 31.2 mg/l (95% confidence interval = 27.8 - 35.0 mg/l);
LC50 (48-hr) = 29.4 mg/l (95% confidence interval = 26.8 - 32.3 mg/l);
LC50 (72-hr) = 28.6 mg/l (95% confidence interval = 25.6 - 31.9 mg/l);
LC50 (96-hr) = 28.6 mg/l (95% confidence interval = 25.6 - 31.9 mg/l)
The Spearman-Karber Trim was 0% for LC50 at 24, 48, 72 and 96 hours.

Test substance : See Section 1.1

DIBC + DMH = 99.4%

Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

16.03.2005 (6)

Type	:	
Species	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 10.326 calculated
Method	:	other: EPIWIN (v 3.10) ECOSAR Submodel (v 0.99g)
Year	:	2003
GLP	:	
Test substance	:	

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg) = 0.19515;
Boiling point (deg C) = 177.85; and
Melting point (deg C) = -65.15.

21.11.2003 (11)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
NOEC	:	17.5 measured/nominal
EC50	:	47.8 measured/nominal
Analytical monitoring	:	no
Method	:	EPA OTS 797.1300
Year	:	2002
GLP	:	yes
Test substance	:	other TS

Method : This study evaluated the acute toxicity of the test substance to <24-hour old daphnia (Daphnia magna Straus) over a 48-hour exposure period under static conditions. A preliminary study found 90 or 100% immobility/mortality at nominal concentrations of 50, 100, 500 and 1000 mg DIBC/L and no effects at 1.0, 2.5, 10, or 25 mg/L after 48 hr. Based on this preliminary study, the test solutions for the definitive study were prepared in duplicate at nominal concentrations of 4.38, 8.75, 17.5, 35.0, 70.0 and 140 mg/l. All concentrations were prepared without correction for purity. Duplicate negative control solutions (dilution water) were maintained concurrently. Dilution water was Lake Huron water supplied to the laboratory by the City of Midland Water Treatment Plant, subsequently sand-filtered, pH-adjusted with gaseous CO2, carbon-filtered and UV-irradiated, adjusted to hardness of 172 mg/l as CaCO3, then autoclaved at 250°F and 18 psi for 30 min. The dilution water used in this study was characterized as follows: TOC < 1000 ug/L, hardness of 172 mg/l as CaCO3, alkalinity of ~38 mg/l as CaCO3, pH of 7.4, conductivity of 390 mmhos/cm and chlorine <1 ug/l. Test vessels were 250-ml glass jars containing 250 ml of test solution. Ten daphnia were impartially introduced to each replicate test vessel at test initiation. Terminal body weight and standard length were recorded for all surviving fish at test termination. Daphnia were observed every 24 hours for immobility, mortality and any other sublethal effects. Immobility was defined as the inability to swim within 15 seconds after gentle agitation of the test container. Dissolved oxygen, pH and temperature were recorded every 24 hours.

The U.S. EPA Probit Program, v. 1.5, using nominal DIBC concentrations, was used to calculate the EC50 values and corresponding slope values. If the Probit Program could not be used, the U.S. EPA Trimmed Spearman-Karber Program, v. 1.5, using nominal DIBC concentrations was used to calculate the EC50 values and corresponding percent trim values. The NOEC was determined as the highest exposure concentration that exhibited 0% mortality or sublethal effects.

Remark : Mortalities in the 140, 70.0 and 35.0 mg/l treatment groups were 100, 85 and 10% after 48 hours of exposure. The death in the 4.35 mg/l treatment group was believed to be accidental, attributed to the organism getting stuck to the vessel side, and was therefore excluded from the statistical evaluation. Immobilization was only reported for 2 daphnia in the 35.0 mg/l treatment group. The light intensity, temperature, pH and dissolved oxygen concentration during this study were maintained at 1784 ± 21 lux, 20.4 ± 0.2°C, 7.5 ± 0.1 and 8.7 ± 0.1 mg/l (or >97% saturation), respectively.

Result : EC50 (24-hr) = 86.2 mg/l (95% confidence interval = 76.1 - 97.6 mg/l; Spearman-Karber Trim = 0%);
EC50 (48-hr) = 47.8 mg/l (95% confidence interval = 40.1 - 57.1 mg/l; Probit slope = 6.5 ± 2.6%)

Test substance : See Section 1.1
DIBC + DMH = 99.4%

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

07.12.2003 (5)

Type :
Species : Daphnia sp. (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 11.922 calculated
Method : other: EPIWIN (v 3.10) ECOSAR Submodel (v 0.99g)
Year : 2003
GLP :
Test substance :

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg) = 0.19515;
Boiling point (deg C) = 177.85; and
Melting point (deg C) = -65.15.

21.11.2003 (11)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : other
Exposure period : 96 hour(s)
Unit : mg/l
Limit test :
Analytical monitoring : no
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 2002
GLP : yes
Test substance : other TS

Method : This study evaluated effects of the test substance on algal growth over a 96-hour exposure period under static conditions. In two range-finding tests of concentrations ranging from 9.38 to 600 mg/L (Test 1) and 0.06 to 600 mg/L (Test 2) the 50% inhibitory effect level was between 9.38 and 18.75

mg/L at 72 and 96 hours. The test solutions were prepared at nominal concentrations of 0.25, 0.61, 1.54, 3.84, 9.6, 24 and 60 mg/l in filter-sterilized algal growth medium. Negative control solutions (medium only) were also maintained concurrently. Test vessels were 250-ml Erlenmeyer flasks plugged w/ foam and contained 50 ml of test solution. Each of four replicated per treatment and control were inoculated with 3-7 day old algal culture to achieve 1E04 cells/ml. Treatment and control solutions were incubated in a growth chamber at 24 ± 2°C under continuous illumination at 8000 ± 20% kLux. Temperature and pH were recorded at test initiation and termination. Cell numbers were measured daily using a haemocytometer. Biomass (as area under the growth curve) and growth rate were calculated from cell counts.

Nominal concentrations of DIBC were used for all calculations. The EC50 values were determined using the TOXSTAT program.

Result : DIBC pH

mg/l	Initial	96-hour
0	7.46	7.94
0.25	7.44	8.06
0.61	7.38	7.95
1.54	7.38	7.86
3.84	7.37	7.92
9.6	7.36	8.04
24	7.30	7.68
60	7.26	7.47

Test Endpoint	Hours	EC50 (95% Conf. Interval)	NOEC (mg/l)	LOEC (mg/l)
Cell Numbers	72	6.97 (5.68, 7.90)	1.54	3.84
Cell Numbers	96	9.41(7.17, 11.87)	3.84	9.6
Biomass *	72	6.62 (5.85, 7.44)	0.25	0.61
Biomass *	96	7.41 (6.55, 8.22)	1.54	3.84
Growth Rate	0-72	19.62 (15.14, 25.43)	3.84	9.6
Growth Rate	0-96	29.95 (25.46, 33.75)	3.84	9.6

* Biomass = area under the growth curve.

Test substance : Purity: DIBC + DMH = 98.34 ± 0.03%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
28.04.2005 (8)

Species : other algae: green algae
Endpoint :
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : = 7.931 calculated
Method : other: EPIWIN (v 3.10) ECOSAR Submodel (v 0.99g)
Year : 2003
GLP :
Test substance :

Remark : The EPIWIN model was run using the following measured physical chemical properties:
Vapor pressure (mm Hg) = 0.19515;
Boiling point (deg C) = 177.85; and
Melting point (deg C) = -65.15.
21.11.2003 (11)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 3560 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	20
Vehicle	:	other: Tergitol 7
Doses	:	1000, 2000, 3980 and 7950 mg/kg body weight
Method	:	other: see remark
Year	:	1948
GLP	:	no
Test substance	:	other TS
Remark	:	A 20% dispersion of the test substance in 1.0% Tergitol 7 was administered by stomach tube to 5 male albino rats per group. Dose concentrations were 1000, 2000, 3980 and 7950 mg/kg body weight. Animals were observed for mortality for 14 days following dosing. Body weights were obtained on the day of dosing and on day 14.
Result	:	LD50 = 3560 mg/kg body weight (95% confidence limit = 1430 to 8860 mg/kg body weight) The compound formed an unstable dispersion with "Tergitol" and the broad range for the LD50 may reflect, in part at least, inaccuracies in the individual doses. The number of deaths are indicated in the following table: Dose (mg/kg) Number dead/number dosed 1000 0/5 2000 2/5 3980 3/5 7950 3/5 No individual clinical signs were provided in the report. All deaths occurred within one to eight days following dosing. Death followed each instance when prostration or narcosis occurred following dosing. All surviving animals gained weight over the 14 days following dosing.
Test substance	:	diisobutyl carbinol - additional information not provided
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

27.04.2005 (2)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other
Value	:	
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	12
Vehicle	:	
Doses	:	saturated vapor or cooled mist (approximately 400 ppm)

Exposure time	:	8 hour(s)
Method	:	other: see remark
Year	:	1948
GLP	:	no
Test substance	:	other TS
Remark	:	Two separate 8-hour inhalation exposure studies were conducted with six rats in each study. In one study, the animals were exposed to a saturated vapor, produced at room temperature. In another study, the test atmosphere was a cooled mist, produced by heating the test substance to 170 degrees C while air was bubbled through it.
Result	:	All 12 rats survived the exposures.
Test substance	:	diisobutyl carbinol - additional information not provided

09.12.2003 (2)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 4591 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	male
Number of animals	:	20
Vehicle	:	other: none
Doses	:	2.52, 5, 10 and 20 ml/kg body weight
Method	:	other: see remark
Year	:	1948
GLP	:	no
Test substance	:	other TS
Remark	:	The undiluted test substance was applied as a single dose to 4 groups of 10 male albino rabbits each at the following dose levels: 2.52, 5.0, 10 and 20 ml/kg, which correlates to doses of 2044, 4056, 8112 and 16,224 mg/kg, respectively (density = 0.8112 g/cm3). The test material was applied, undiluted at the appropriate dose, under an impervious sheeting. The animals remained exposed to the test substance for 24 hours. Rabbits were observed for 14 days and body weights were obtained on the day of application and on day 14.
Result	:	LD50 = 4591 mg/kg body weight (95% confidence limits = 2036 to 10383 mg/kg body weight). The number of deaths are indicated in the following table:

Dose (ml/kg)	Number dead/number dosed
2.52	1/5
5	2/5
10	4/5
20	4/5

		All deaths occurred between 2 and 11 days following application. Marked erythema and in some instances, necrosis of the skin were noted. Livers showed varying degrees of congestion and the kidneys were usually pale. All surviving rabbits lost weight over the 14 day post-exposure period.
Test substance	:	diisobutyl carbinol - additional information not provided
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

09.12.2003 (2)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	other: Crl: CD(SD)
Route of admin.	:	gavage
Exposure period	:	See Section 5.8.1
Frequency of treatm.	:	See Section 5.8.1
Post exposure period	:	See Section 5.8.1
Doses	:	50, 150, 500 mg/kg/day (in 0.5% methocel A4M)
Control group	:	yes, concurrent vehicle
NOAEL	:	= 50 mg/kg bw
LOAEL	:	= 150 mg/kg bw
Method	:	other: OECD 422 and US EPA OPPTS 870.3650
Year	:	2006
GLP	:	yes
Test substance	:	other TS
Remark	:	See Section 5.8.1.
Test substance	:	Diisobutyl Carbinol (DIBC): a mixture of 2,6-Dimethyl-4-heptanol and 4,6-Dimethyl-2-heptanol, Lot Number AA0155T3YY, Purity: 99.1%.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

18.05.2006 (1)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537; Escherichia coli tester strain WP2uvrA.
Test concentration	:	3.33, 10.0, 33.3, 100, 333 and 1000 ug/plate (with S9 mix); 1.00, 3.33, 10.0, 33.3, 100 and 500 ug/plate (without S9 mix)
Cycotoxic concentr.	:	>= 333 ug/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: EEC Directive 2000/32/EC; OECD Method 471; U.S. EPA OPPTS Method 870.5100.
Year	:	2002
GLP	:	yes
Test substance	:	other TS
Method	:	The preincubation assay was conducted with six concentrations of DIBC in both the presence and absence of microsomal enzymes prepared from

Aroclor™-induced rat liver (S9 mix) along with concurrent vehicle and positive controls using three plates per concentration. A range finding study was conducted with strains TA-100 and WP2uvrA at 10 DIBC concentrations ranging from 6.67 to 5000 ug/plate with and without metabolic activation. Reduced or absent background lawn was observed at concentrations of 333 ug/plate and higher in both systems. The six concentrations tested in the mutagenicity assay with all tester strains ranged from 3.33 to 1000 ug per plate in the presence of S9 mix and from 1.00 to 500 ug per plate in the absence of S9 mix. Dimethylsulfoxide (DMSO) was the solvent for the test substance and served as the negative control. For the non-activation assay, the following positive control substances were used: Sodium azide (for strains TA1535 and TA100); 2-Nitrofluorene (for strain TA98); ICR-191 (for strain TA1537) and 4-nitroquinoline-N-oxide (for strain WP2uvrA). The positive control substance, 2-aminoanthracene was used for all tester strains with metabolic activation. The results of the initial mutagenicity assay were confirmed in an independent experiment.

The criteria for evaluation were: at least a 2-fold (TA-100) or 3-fold (TA98, TA1535, TA1537, and WP2uvrA) concentration-related increase and reproducible increase in mean revertants per plate over the mean of the appropriate vehicle control was considered positive.

Result : No increase in revertants meeting the criteria for positive response was observed at any concentration in any strain with or without metabolic activation in either experiment. Under the conditions of this study, DIBC was not mutagenic to bacterial cells with or without metabolic activation.
Test substance : See Section 1.1: Purity: DIBC + DMH = 98.34%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.03.2005 (7)

Type : Chromosomal aberration test
System of testing : Rat Lymphocytes
Test concentration : 0, 360, 720, and 1440 ug/ml (without S-9, 4-hour treatment); 0, 90, 180, and 360 ug/ml (with S-9, 4-hour treatment); and 0, 22.5, 45, and 90 ug/ml (without S-9, 24 hour treatment)
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: OECD Guideline No. 473, Genetic Toxicology: In vitro Mammalian Cytogenetic Test.EPA OPPTS 870.5375, In vitro Mammalian Chromosome Aberration.Directive EC B.10, 2000, Mutagenicity: In vitro Mammalian Chromosomal Aberration Test.
Year : 2004
GLP : yes
Test substance : other TS

Remark : The criteria for positive response were significant dose-related and reproducible increase in the frequency of cells with aberrations.
Result : In the toxicity assay, the four hour treatment without metabolic activation, had reductions in mitotic indices at the two highest concentrations of 720 (30% reduction) and 1440 (39% reduction) ug/ml. The remaining cultures had reductions in mitotic indices of 0 to 19%.
With metabolic activation, the 720 and 1440 ug/ml cultures had no mitotic indices and the 360 ug/ml culture had a 60% reduction in mitotic index. The remaining cultures had reductions in mitotic indices of 0 to 19%.
Cultures treated for 24 hours without activation had no mitosis at 360, 720 and 1440 ug/ml, a 95% reduction at 180 ug/ml and a 52% reduction at 90 ug/ml.
The remaining cultures had reductions in mitotic indices of 13 to 25%.
There were no significant increases in the frequency of cells with aberrations in cultures treated for 4 hours with activation or 24 hours

without activation.
In the first assay without activation and 4-hour treatment, a statistically significant trend in the incidence of cells with aberrations was observed (3.5% at 1440 ug/ml compared to 0.5, 0.5 and 1.5% at 0, 360 and 720 ug/ml, respectively). No statistical differences were found in the repeat assay, and it was concluded that the original finding was not biologically significant.

Test condition : Blood samples were collected from male rats by cardiac puncture. In each assay, the blood samples were pooled and whole blood cultures were set up by the addition of the appropriate medium and supplements. Cell cultures were treated for 4 hours in the presence and absence of Aroclor™-induced rat liver (S-9 mix) and for 24 hours without the S-9 mix at dose concentrations of , 22.5, 45, 90, 180, 360, 720 and 1440 ug/ml of test substance. Based on the mitotic indices, the following concentrations were used to determine chromosomal aberrations: 0, 360, 720, and 1440 ug/ml (without S-9 for 4 hour treatment), 0, 90, 180, and 360 ug/ml (with S-9 for 4 hours), and 0, 22.5, 45, and 90 ug/ml (without S-9 for 24 hours). All test assays were performed along with concurrent vehicle and positive controls. Dimethylsulfoxide (DMSO) was the solvent for the test substance and served as the negative control. For the non-activation assay, Mitomycin C was the positive control substance: The positive control substance cyclophosphamide was used in the activation assay. After the incubations, the cells were washed, swollen by hypotonic treatment, fixed to slides and stained. The cells were scored for structural chromosomal abnormalities, such as chromatid and chromosome gaps and chromatid breaks and exchanges. The four hour activation assay without S-9 mix was repeated at concentrations of 0, 100,200, 300, 400, 600, 800, 1000, 1200 and 1440 ug/ml because of a statistical finding in the original assay. The concentrations used for determination of chromosomal abnormalities were 0, 200, 300 and 1440 ug/ml.

Test substance : See Section 1.1: Purity: DIBC + DMH = 98.34%
Conclusion : DIBC was not considered genotoxic in this test.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
21.08.2006 (4)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type : other
Species : rat
Sex : male/female
Strain : other: Crl: CD(SD)
Route of admin. : gavage
Exposure period : Males: 34 days, Females: 14 days before mating to day 4 of lactation
Frequency of treatm. : daily
Premating exposure period
Male : 2 weeks
Female : 2 weeks
Duration of test : males 10 days post-mating; females lactation day 4.
No. of generation studies : 2
Doses : 50, 150, 500 mg/kg/day (in 0.5% methocel A4M)
Control group : yes, concurrent vehicle

NOAEL parental	:	= 50 mg/kg bw
NOAEL F1 offspring	:	>= 500 mg/kg bw
other: NOAEL Neurological	:	>= 500 - mg/kg bw
Method	:	other: OECD Guideline No. 422, A Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test.U.S. EPA OPPTS 870.3650, Combined repeated dose toxicity study with the reproduction/developmental toxic
Year	:	2006
GLP	:	yes
Test substance	:	other TS

Remark : STATISTICAL ANALYSIS: Descriptive statistics (means and standard deviations) were reported for RBC indices and WBC differential counts. Parental body weights and weight gains, litter mean body weights, feed consumption, urine volume, urine specific gravity, coagulation, clinical chemistry data, appropriate hematologic data and organ weights (absolute and relative) were first evaluated by Bartlett's Test for equality of variances. Based on the outcome, a parametric or nonparametric test analysis of variance (ANOVA) was performed. If the ANOVA was significant (alpha=0.05), then a Dunnett's Test or the Wilcoxon Rank-Sum Test with Bonferroni's correction was performed. The gestation length, average time to mating and litter size were examined with a non-parametric ANOVA. If there was significance, the Wilcoxon Rank Sum Test with Bonferroni's correction was performed. Statistical outliers were identified by a sequential method and were only excluded from the analysis for documented, scientifically sound reasons. The mating, conception, fertility and gestation indices were analyzed by the Fisher exact probability test with Bonferroni's correction. Evaluation of the neonatal sex ratio on lactation day (ld) 1 was performed by the binomial distribution test. Survival indices, post-implantation loss and other incidence data among neonates were analyzed using the litter as the experimental unit by the censored Wilcoxon test as modified by Haseman and Hoel with Bonferroni's correction. DCO and sensory evaluation incidence scores were statistically analyzed by a z-test of proportions comparing each treated group to the control. Data collected at each time point were analyzed separately. Rectal temperature and grip performance were analyzed by ANCOVA with exposure as the factor and the covariate of the pre-exposure time point measure of the variable. The first examination of the ANCOVA was for the treatment by pre-exposure measure interaction and if this was significant, then an ANVOA was run separately for each time point. If the dose effect was significant, the least square means were generated and a t-test performed. Motor activity counts were reported as their square roots and analyzed by a repeated-measure design with treatment as the factor and the repeated factor of time. Motor activity also had the repeated factor of epoch (within time) in the model. The inclusion of pre-exposure data in the analysis made relevant only the analyses that included factors of both treatment and time. The primary interactions examined were treatment-by-time and treatment-by-time-by-epoch. Linear contrasts were calculated to determine which treatment groups differed from the control if either of these interactions were significant. The probability values were reported without correction.

Result : ANALYTICAL ANALYSIS:

-Concentrations: Analyses of the dosing concentrations from the initial preparation indicated mean concentrations of DIBC ranging from 99.2-104% of the targeted concentrations.
-Stability: DIBC in 0.5% methylcellulose was found to be stable for 25 and 64 days at concentration ranging from 2.5 and 250 mg/ml.
-Homogeneity: Analysis of aliquots removed from the low and high dose groups confirmed that DIBC was homogenously distributed throughout the dose suspension.

PARENTAL TOXIC EFFECTS BY DOSE LEVEL:
-Mortality and day of death: none

-In-Life Observations: Oral administration of DIBC resulted in increased salivation (perioral staining - clear) at the 500 mg/kg dose level in both sexes. Salivation was transient, as it was usually observed only after dosing, suggesting a local response to the taste of the test material.

Salient Male Clinical Observations

Male Clin Obs	Dose Level (mg/kg/day)			
(# Animals Affected)	0	50	150	500
Perioral Soiling - Clear	0	0	0	10*

* indicates effects considered to be treatment-related.

Salient Female Clinical Observations

Female Clin Obs	Dose Level (mg/kg/day)			
(# Animals Affected)	0	50	150	500
Perioral Soiling - Clear	0	0	0	4*

* indicates effects considered to be treatment-related.

-Detailed Clinical Observations: Except as noted above, examinations performed on all rats revealed no treatment-related or statistically significant findings in the treatment groups as compared to the control group in either sex.

-Body weight/body weight gain: No treatment-related differences in body weight or weight gain were observed for males at any dose level throughout the study. Body weights of the high-dose group females were slightly lower than those of the controls beginning on gd 14 of the gestation phase (=< 7.2%) and continued through the lactation phase (=< 7.8%), achieving statistical significance on ld 4. During the gestation phase of the study, there was a decrease in body weight gains on gd 7-14 relative to the controls in dams given 500 mg/kg/day. Although not statistically significant, there was also a negative weight gain on ld 1-4 in females given 500 mg/kg/day. There were no effects of DIBC at 50 or 150 mg/kg/day on female body weight or body weight gains during any phase of the study.

Gestation and Lactation Body Weight Data

	Mean Body Weight (g) Dose Level (mg/kg/day)			
Study Day	0	50	150	500
gd 14	316.0	303.1	309.2	291.8*
gd 20	389.3	376.2	381.2	361.3*
ld 1	292.2	283.1	293.0	275.8*
ld 4	295.6	285.9	295.4	272.5*#

* indicates effects considered to be treatment-related.
# Statistically different from control mean, alpha = 0.05.

Gestation and Lactation Body Weight Gains

	Mean Body Weight Gains (g) Dose Level (mg/kg/day)			
Study Day	0	50	150	500

gd 7-14	41.4	38.0	38.1	28.4*#
gd 14-20	73.2	73.1	72.0	69.5*
gd 0-20	151.2	148.5	149.1	135.2*
ld 1-4	3.5	2.8	2.3	-3.3*

* indicates effects considered to be treatment-related.
# Statistically different from control mean, alpha = 0.05.

-Feed Consumption: There were no treatment-related effects on male food consumption at any exposure level. Mean food consumption of females given 500 mg/kg/day was significantly decreased (10.2%) on days 1-7 of the premating phase. Feed consumption was also slightly decreased for the high-dose females during the last two weeks of gestation (=< 8.9%) and during the lactation phase (10.8%) of the study. Although not statistically significant, these decreases coincided with the deceases observed in body weight for the high-dose females and were therefore considered treatment-related. There were no treatment-related effects on the food consumption values for the females in the 50 and 150 mg/kg/day groups.

-Reproductive Indices, Pup Survival and Sex Ratio: There were no treatment-related effects at any dose level on any of the reproductive indices, time to mating, gestation length, postimplantation loss, pup survival or pup sex ratio. Postimplantation loss was numerically higher in females dosed at 150 and 500 mg/kg/day, but not significantly different from controls and was considered normal variability. The 150 and 500 mg/kg/day postimplantation loss values (7.33 and 8.59%, respectively) were within range of the historical control data and no adverse gross or histological findings were present in the reproductive organs of the females at these dose levels. There was a statistically identified difference in the sex ratio of pups in the 150 mg/kg/day dose group that was not considered toxicologically significant because the sex ratio was not altered at 500 mg/kg/day.

Historical Control Data for Postimplantation Loss

Study Number	1	2	3	4	5	6	7
Year	2000	2003	2004	2004	2005	2005	2005
Post-Implantation Loss (%)	6.2	5.69	3.72	5.43	8.04	9.10	10.85

Range 3.72 - 10.85 %

Sex Ratio

	Dose Level (mg/kg/day)			
	0	50	150	500
Sex Ratio (%)	54:46	51:49	41:59*	49:51

* Statistically different from expected value of 50% by the Binomial Distribution Test.

-Litter Observations: Observations recorded in the offspring occurred at low frequency and bore no relationship to treatment.

-Litter Size and Pup Body Weights: There were no treatment-related effects on litter size or pup body weights at any dose level tested.

FUNCTIONAL TESTS:
-Sensory Evaluation: Examinations of males and females at baseline and following treatment (at termination) revealed no treatment-related findings.
-Rectal Temperature: Treatment did not affect the rectal temperature of either sex.
-Grip Performance: There were no treatment-related effects on the hindlimb or forelimb grip performance in either males or females.
-Motor Activity: Treatment did not affect total motor activity count in either sex. The distribution of the motor activity counts within a session were also not affected by treatment in females but was significant in males. For interpretation of this statistically significant triple interaction, additional examination of the data was performed. For all of the double interactions containing treatment, time or epoch were examined and indicated that there was a significant difference in time-epoch, but that it was due to a difference in days, not treatment. The male data for overall count distributions for the four treatment groups displayed differences from baseline and post-treatment conditions, irrespective of treatment. Linear contrasts indicated that that triple interactions were not statistically significant. The interpretation of these data led to the conclusion that the statistically significant triple interaction in male rats represents a difference between days rather than an effect of treatment.

CLINICAL PATHOLOGY
-Hematology: There were no treatment-related alterations in hematologic parameters of males or females at any dose level.
-Coagulation: There were no treatment-related alterations in prothrombin times of males or females at any dose level.
-Clinical Chemistry: Males and females treated at 500 mg/kg/day had higher mean total protein and cholesterol concentrations that were statistically identified and interpreted to be treatment-related. A statistically significant increase in mean cholesterol in males treated at 50 mg/kg/day was considered non-treatment-related as there was no dose response. A statistically significant decrease in creatinine levels in the 500 mg/kg/day females was considered to not be treatment-related because of the minimal difference from the control group and the lack of an effect on creatinine levels in all males.

Salient Clinical Chemistry Findings

mg/kg/day:	0	Historical^	50	150	500
			MALES		
Mean Total Protein (mg/dl)	6.5	6.2 - 6.6	6.8	6.7	7.0*#
Mean Cholesterol (mg/dl)	38	42 - 58	48~	46	69*~
			FEMALES		
Mean Total Protein (mg/dl)	7.1	6.5 - 7.2	7.1	7.2	7.4*#
Mean Cholesterol (mg/dl)	50	42 - 73	49	57	71*#

^ Historical controls group mean range from recent OECD 422 studies.
* indicates effects considered to be treatment-related.
# Statistically different from control mean by Dunnett's test, alpha = 0.05.
~ Statistically different from control mean by Wilcoxon's test, alpha = 0.05.

-Urinalysis: As per test guideline, urinalysis was not performed in females. The only treatment-related effect on urinalysis parameters in males was a slight, dose-responsive decrease in urine pH at all dose levels. There was no evidence of renal toxicity, therefore this decrease was most likely due to the excretion of acidic metabolites of DIBC.

Salient Urinalysis Findings in Males

Dose (mg/kg/day)	0	50	150	500
Urine pH	7.5 (5) 8.0 (2) 8.5 (4) 9.0 (1)	7.0 (4) 7.5 (6) 8.0 (1) 8.5(1)	6.5 (1) 7.0 (8) 7.5 (2) 8.0 (1)	6.0 (1) 6.5 (3) 7.0 (7) 7.5 (1)

Urine pH data tabulated as number of animals (N) with the stated value.

ANATOMIC PATHOLOGY:
-Terminal Body and Organ Weights: Females treated at 500 mg/kg/day had a statistically significant lower mean final body weight that was considered treatment-related. Treatment-related statistically significant increases in mean absolute liver weights were noted in males of the middle (17% increase) and high dose (28% increase) groups, as well as the high dose females (10% increase). These changes correlated with increases in relative liver weights that were also statistically significant as compared to controls. The higher liver weights corresponded with very slight liver hypertrophy of centrilobular hepatocytes in males at 150 or 500 mg/kg/day and females at 500 mg/kg/day. Males treated at 500 mg/kg/day and females treated at 150 or 500 mg/kg/day had higher relative kidney weights (statistically significant increases for females at both dose levels) that were considered treatment-related. There were no corresponding clinical pathologic or histopathologic alterations for the increase kidney weights. Females in the 500 mg/kg/day group had increased mean absolute and relative (statistically significant) adrenal weights. The higher adrenal weights were considered normal variation based on the lack of consistency in individual adrenal weights at this dose level, the absence of any treatment-related histopathologic effects and the lack of a similar weight increase in the males at any dose level. Males treated with 50 mg/kg/day had a statistically significant decrease in mean relative adrenal weight that was considered normal variation due to the lack of a dose response.

Salient Final Body Weight and Organ Weight Effects

mg/kg/day:	0	Historical^	50	150	500
			MALES		
Final Body Weight (g)	375.0	354.1-447.2	385.5	401.1	383.7
Relative Adrenals (g/100 g bw)	0.017	0.014-0.021	0.014#	0.015	0.016
Relative Kidneys (g/100 g bw)	0.763	0.713-0.801	0.740	0.773	0.822*
Absolute Liver (g)	10.519	10.108-13.420	11.469	12.278*#	13.421*#
Relative Liver (g/100 g bw)	2.800	2.719-3.298	2.972	3.062*#	3.493*#
			FEMALES		
Final Body Weight (g)	277.5	251.2-290.4	268.0	278.3	258.8*#
Absolute Adrenals (g)	0.089	0.070-0.094	0.084	0.079	0.132
Relative Adrenals (g/100 g bw)	0.032	0.027-0.037	0.031	0.029	0.051~
Relative Kidneys (g/100 g bw)	0.686	0.696-0.742	0.741	0.755*#	0.773*#

Absolute Liver (g)	9.882	8.185-10.433	9.714	10.315	10.860*
Relative Liver (g/100 g bw)	3.557	3.155-3.748	3.628	3.696	4.195*#

^ Historical controls groups mean range from recent OECD 422 studies.
* indicates the effects were considered to be treatment-related.
# Statistically different from control mean by Dunnett's Test, alpha = 0.05.
~ Statistically different from control mean by Wilcoxon's Test, alpha = 0.05.

-Gross Pathology: There were no treatment-related gross pathologic observations for either sex at any dose level tested.
-Histopathology: Males treated with DIBC at 150 or 500 mg/kg/day and females treated with DIBC at 500 mg/kg/day had treatment-related increases in the incidence of very slight hypertrophy of the centrilobular hepatocytes. The hypertrophy corresponded to the increased liver weights at these dose levels. There were no accompanying degenerative, necrotizing or inflammatory effects of the liver. Some males and females from all dose levels had treatment-related degeneration and/or inflammation of the olfactory epithelium of the nasal tissues. The severity and incidence of these alterations were dose responsive, with 1, 2, and 6 males and 1, 3 and 4 females affected in the 50, 150 and 500 mg/kg/day groups, respectively. The respiratory epithelium of the nasal tissues also had degradation and/or inflammation in some males and females given 500 mg/kg/day. The degenerative and inflammatory effects were neither uniform in distribution, nor anatomically specific as would be expected of a system targeted by the systemic route. Hence, these findings were considered to be the result of local irritation of the test material which inadvertently refluxed back into the nasal passages during the gavage process. All other histopathologic observations were interpreted to be spontaneous or iatrogenic alterations, unassociated with the administration of DIBC.

Treatment-Related Histopathologic Effects

Sex	Males				Females			
Dose (mg/kg/day)	0	50	150	500	0	50	150	500
LIVER (No. examined)	12	12	12	12	12	12	12	12
Hypertrophy, hepatocyte, centrilobular:								
very slight	2	0	5*	9*	1	1	1	10*
PHARYNX								
(No. examined)	12	12	12	12	12	12	12	12
Degeneration, olf. epi., multi								
very slight	1	0	0	0	1	0	1	0
Degeneration, olf. epi., multifocal								
very slight	0	1*	1*	3*	0	1*	3*	1*
slight	0	0	1*	0	0	0	0	0
Degeneration of olf. and resp. epi., multifocal								
slight	0	0	0	1*	0	0	0	1*
moderate	0	0	0	2*	0	0	0	2*
Inflammation, acute, olf., epi., focal								
very slight	0	0	0	1*	0	0	0	0
Inflammation, acute, olf. epi.., multifocal								
very slight	0	1*	1*	1*	0	1*	0	1*
Inflammation, acute, olf. & resp. epi., multifocal								
slight	0	0	0	3*	0	0	0	2*
Total animals with nasal lesions	0	1*	2*	6*	0	1*	3*	4*

* indicates the effects considered to be treatment related.

Test condition : TEST ORGANISMS-Male and female CD rats-Age: ~8 weeks of age-Number of animals: 48 females and 48 males (12 sex/group)

ADMINISTRATION/EXPOSURE
-Route: oral/gavage-Doses: The target doses were 0, 50, 150 and 500 mg DIBC/kg/day. DIBC was administered in a 0.5% METHOCEL A4M vehicle and samples were analyzed to confirm homogeneity, stability and concentration verification.
-Exposures: Once Daily
Males- 2 weeks prebreeding, two weeks breeding and up to necropsy on day 34
Females- 2 weeks prebreeding, two weeks breeding, through gestation (3 weeks) and lactation (4 days)

PARAMETERS ASSESSED DURING STUDY:
-Clinical observations performed and frequency: Clinical observations were conducted daily throughout the study period.
-Detailed Clinical Observations (DCO): Conducted on all rats pre-exposure and weekly throughout the study. Mated females received DCO examinations on gestation day (gd) 0, 7, 14 and 20, and lactation day (ld) 3. The DCOs included cage-side, hand-held and open-field observations that were recorded categorically or using explicitly defined scales.
-Functional Tests: The functional tests included a sensory evaluation (nocioception and startle response), rectal temperature, grip performance and motor activity.
-Body weight/body weight gain: All rats were weighed at least once in the pre-exposure period and on day 0 prior to dosing. Male body weights were recorded weekly throughout the study. Female body weights were performed weekly for the premating and mating periods. Maternal body weights were recorded on GD 0, 7, 14, 17 and 20. Females that delivered were weighed on ld 1 and 4. Females that failed to mate or deliver were weighed on a weekly basis for the study duration.
-Food consumption: Food consumption was determined weekly for males and females during the pre-mating period. Due to co-housing, food consumption was not measured during mating. Following breeding, food consumption was not measured for the males. During gestation, food consumption for the females was measured on gd 0, 7, 14, 17 and 20. After parturition, food consumption was measured on ld 1 and 4. Food consumption was not recorded for females that did not mate or deliver.
-Breeding Procedures: During the 2 week mating period, one male and one female from the same dose group were co-habitated until pregnancy occurs or the mating period is over. Females were examined daily for a vaginal copulatory plug or the vaginal presence of sperm determined by vaginal lavage samples. If pregnancy was not determined by the end of the mating period, the animals were separated and housed individually for the remainder of the study.
-Litter Data: Females were observed for signs of parturition beginning on gd 20. The first day the presence of a litter was noted was designated ld 0. All litters were examined as soon as possible after delivery and the following information was recorded: date of parturition, litter size on ld 0, the number of live and dead pups on ld 0, 1 and 4 post-partum and the sex and weight of each pup on ld 1 and 4. Pup clinical observations were recorded on post-natal day(pnd) 0, 1 and 4. In addition, any physical abnormalities or demeanor changes were recorded during the lactation period. Any pups found dead were sexed, examined grossly for external and visual effects, if possible and discarded.

PATHOLOGY:
-Clinical Pathology: On the day prior to necropsy, all animals were fasted overnight. At necropsy, animals were anesthetized with carbon dioxide and blood samples were removed from the orbital sinus. Blood samples

were not taken from females that failed to deliver a litter.
--Hematology Assays: hematocrit (HCT), hemoglobin concentration (HGB), red blood cell (RBC) count, total white blood cell (WBC) count, platelet (PLAT) count, reticulocyte (RET) count, and red blood cell indices including mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC).
--Coagulation Assay: prothrombin time (PT).
--Clinical Chemistry Assays: Enzyme activities of alkaline phosphatase (AP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and concentrations of albumin (ALB), cholesterol (CHOL), creatinine (CREAT), electrolytes (Na, K, PHOS, Cl and Ca), glucose (GLU), total bilirubin (TBIL), total protein (TP), triglycerides (TRIG) and urea nitrogen (UN).
--Urinalysis Assays: Urine was collected from all male rats in each dose group during the week prior to necropsy. Animals were housed overnight in metabolic cages. Urine was evaluated for: Color, appearance, specific gravity, and urine volume. Semiquantitative analysis: pH, bilirubin, glucose, proteins, ketones, blood, and urobilinogen. A microscopic characterization of microsediment was also performed.
-Anatomic Pathology: A complete necropsy of all animals was performed. Male rats were necropsied on study day 34. Females that delivered were necropsied on ld 5. Female rats that did not deliver were necropsied at least 24 days after the last day of the mating period. The necropsy included an examination of: the external tissues and all orifices, the cranial, nasal, thoracic and abdominal cavities, and all viscera. Selected tissues of the viscera were incised.
--Examination of uterus: The uteri of all females were stained and examined for the presence and number of implantation sites.
--Organ weights: The following organs were trimmed and weighed: adrenals, brain, epididymides, heart, kidney, liver, spleen, testes, thymus, and thyroid with parathyroids (weighed after fixation)
-Histopathology: Histological examinations were conducted on numerous tissues, including tissues exhibiting gross lesions, from all adult rats in the control and high-dose groups, as well as any rats found dead or sacrificed moribund. The histopathological examination of the testes included a qualitative assessment of the stages of spermatogenesis. Microscopic evaluation involved a qualitative assessment of the relationships between spermatogenia, spermatocytes, spermatids and spermatozoa in the seminiferous tubules. Sections of the testes were also examined for the presence of degenerative changes. Also, the liver, kidneys and nasal tissue-pharynx were examined at all dose levels for both sexes as significant findings were present between the control and high-dose group.

Test substance : Diisobutyl Carbinol (DIBC): a mixture of 2,6-Dimethyl-4-heptanol and 4,6-Dimethyl-2-heptanol, Lot Number AA0155T3YY, Purity: 99.1%.

Conclusion : A no-observed effect level (NOEL) for general toxicity was 50 mg/kg/day. The NOEL for reproductive and neurological effects was 500 mg/kg/day, the highest dose tested.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

21.08.2006 (1)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT